

Human Papillomavirus-Associated Cancers in Patients With Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

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For the AIDS–Cancer Match Registry Study Group

Background: Human papillomavirus (HPV)-associated anogenital malignancies occur frequently in patients with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). The purpose of our study was to determine if the high frequency of these cancers is due to lifestyle factors associated with both HPV and HIV infections or to immunosuppression following HIV infection. **Methods:** We studied invasive and *in situ* HPV-associated cancers among 309 365 U.S. patients with HIV infection/AIDS (257 605 males and 51 760 females) from 5 years before the date of AIDS onset to 5 years after this date. Sex-, race-, and age-standardized ratios of observed-to-expected cancers served as measures of relative risk (RR). Trend tests were used to evaluate changes in the RRs during the 10 years spanning AIDS onset. All statistical tests were two-sided. **Results:** All HPV-associated cancers in AIDS patients occurred in statistically significant excess compared with the expected numbers of cancers. For *in situ* cancers, overall risks were significantly increased for cervical (RR = 4.6; 95% confidence interval [CI] = 4.3–5.0), vulvar/vaginal (RR = 3.9; 95% CI = 2.0–7.0), anal (in females, RR = 7.8 [95% CI = 0.2–43.6]; in males, RR = 60.1 [95% CI = 49.2–72.7]), and penile (RR = 6.9; 95% CI = 4.2–10.6) cancers, and RRs increased during the 10 years spanning AIDS onset for carcinomas *in situ* of the cervix (*P* for trend <.001), vulva/vagina (*P* for trend = .04), and penis (*P* for trend = .04). For invasive cancers, overall risks were significantly increased for cervical (RR = 5.4; 95% CI = 3.9–7.2), vulvar/vaginal (RR = 5.8; 95% CI = 3.0–10.2), and anal (RR = 6.8; 95% CI = 2.7–14.0) cancers in females and for anal (RR = 37.9; 95% CI = 33.0–43.4), penile (RR = 3.7; 95% CI = 2.0–6.2), tonsillar (RR = 2.6; 95% CI = 1.8–3.8), and conjunctival (RR = 14.6; 95% CI = 5.8–30.0) cancers in males. However, RRs for invasive cancers changed little during the 10 years spanning AIDS onset. **Conclusions:** HPV-associated malignancies occur at increased rates in persons with HIV/AIDS. Increasing RRs for *in situ* cancers to and beyond the time of AIDS onset may reflect the gradual loss of control over HPV-infected keratinocytes with advancing immunosuppression. However, the lack of a similar increase for invasive HPV-associated cancers suggests that late-stage cancer invasion is not greatly influenced by immune status. [J Natl Cancer Inst 2000;92:1500–10]

Patients with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are at increased risk of developing certain cancers, notably Kaposi's sarcoma and non-Hodgkin's lymphoma (1,2). In a large study of the general cancer spectrum among patients with AIDS, Goedert

et al. (3) suggested that AIDS may also lead to significantly increased rates of other cancers, including Hodgkin's disease and possibly multiple myeloma, brain cancer, and seminoma. Human papillomavirus (HPV)-associated malignancies have been reported to occur in excess among patients with HIV or AIDS. These malignancies include squamous intraepithelial lesions (SILs) and invasive cancers of the cervix (3) and anus (4) as well as conjunctival carcinoma (5). It is not clear, however, whether the excess of these cancers reflects increased HPV exposure, a high prevalence of other cofactors among patients with HIV/AIDS, or a genuine role of HIV-related immunosuppression in HPV-induced carcinogenesis. To clarify the associations, we used data from the recently updated multicenter AIDS–Cancer Match Registry Study in the United States to investigate in detail the patterns of HPV-associated malignancies among 309 365 patients with AIDS.

SUBJECTS AND METHODS

Matching of AIDS and Cancer Data

Data from AIDS and cancer registries in 11 state and metropolitan locations were linked between 1995 and 1998. Approximately one third of the U.S. population lived in these linkage areas (Table 1). General principles in the linkage procedure have been described elsewhere (6). Our present study differed from the previous study, since it used a commercially available package for matching. We used software (Automatch® versions 3.0 and 4.1; MatchWare Technologies Inc., Burtonsville, MD) to implement a probabilistic matching algorithm that weighed the likelihood of subject identity on the basis of identical or near-identical information in AIDS and cancer registries. The rank order of weight in the algorithm included, when available, the following: Social Security number; last name; first name; middle name or initial; the soundex codes¹ for the last name, first name, and middle name or initial; birth and death dates; race; sex; and home address. Locally situated AIDS and cancer registrars reviewed manually all matches scored by the algorithm as questionable to determine match status. All personal identifiers were removed from the data prior to being sent outside the linkage sites. Ethical and legal reviews at all participating AIDS and cancer registries ensured that patient confidentiality was maintained.

After the AIDS and cancer registry data were linked, the time of AIDS onset was backdated to the date of an AIDS-defining cancer in the cancer registry up

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See "Appendix" section for list of contributors and participants in the AIDS–Cancer Match Registry Study Group.

See "Notes" following "References."

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Table 1. Background information on acquired immunodeficiency syndrome (AIDS) and cancer registries contributing data to the AIDS–Cancer Match Registry on human papillomavirus (HPV)-associated cancers

Area	Population covered in 1990, million*	Period covered by both AIDS and cancer registries	No. of AIDS patients in AIDS registry†		No. of HPV-associated cancers in cancer registry‡		No. of HPV-associated cancers in AIDS patients in AIDS–Cancer Match Registry§	
			Men	Women	Men	Women	Men	Women
Atlanta (GA)	2.2	05/1980–12/1994	11 803	1771	439	8683	9	16
Connecticut	3.3	11/1980–09/1995	6270	1876	813	14 901	2	83
Florida	13.0	01/1981–12/1995	43 551	10 757	4078	41 306	70	213
Illinois	11.4*	01/1980–12/1995	15 330	2186	1964	34 180	26	19
Los Angeles (CA)	8.9	03/1978–02/1996	31 458	2031	2504	41 696	85	67
Massachusetts	6.0	01/1982–12/1995	9551	2114	1334	11 271	17	55
New Jersey	7.8	01/1979–12/1996	24 887	9273	2205	30 783	40	282
New York City/State	18.0	01/1981–12/1994	81 375	20 403	3935	48 343	76	389
San Diego (CA)	2.5	01/1988–12/1995	6674	453	339	4480	8	3
San Francisco (CA)	3.7	01/1980–09/1995	21 858	698	1242	18 263	88	20
Seattle (WA)	3.4	01/1983–06/1996	4848	198	746	20 475	11	7
Total	80.2	03/1978–12/1996	257 605	51 760	19 599	274 381	432	1154

*In the generation of common background cancer incidence rates for the 11 areas covered, cancer rates for Illinois were substituted by Surveillance, Epidemiology, and End Results rates for Detroit (MI) and Iowa (1990 population, 6.7 million). Atlanta data included only first cancer diagnoses. Massachusetts data were excluded from *in situ* cancer assessments because this registry does not collect such data.

†Number of AIDS patients during period covered by both the AIDS and cancer registries.

‡Number of HPV-associated cancers during the period covered by both the AIDS and cancer registries. HPV-associated cancers include invasive and *in situ* cancers of the cervix, vulva/vagina, anus, and penis and invasive conjunctival and tonsillar cancers.

§Number of HPV-associated cancers in AIDS patients during the period from 60 months before to 60 months after AIDS.

to 5 years before the recorded date in the AIDS registry. We considered Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer as AIDS-defining cancers among HIV-infected individuals, according to the expanded 1993 AIDS surveillance case definition of the U.S. Centers for Disease Control and Prevention (7). Specifically, for 5167 patients (1.7%), the AIDS onset date was reset because of an earlier diagnosis of Kaposi's sarcoma (median change, 5 months). For 1752 patients (0.6%), the AIDS onset date was reset because of an earlier non-Hodgkin's lymphoma (median change, 3 months), and 182 patients (0.06%) had their AIDS onset date reset because of an earlier diagnosis of invasive cervical carcinoma (median change, 13 months).

HPV-Associated Cancers

This article focuses on possible HPV-associated squamous cell carcinomas. First, we excluded all cancers that were either Kaposi's sarcoma (histology code 9140) or lymphoma or leukemia (histology codes 9590–9989) according to the International Classification of Diseases for Oncology, 2nd edition (ICD-O2) (8). We then applied the following ICD-O2 restrictions to define the invasive (behavior code 3) cancers under study: uterine cervix (topography C530–C539 with any histology except adenocarcinoma: 8140–8340), anus (C209–C218 with histologies 8050–8076, 8094, or 8120–8124), vulva/vagina (C510–C529 with histologies 8050–8076, 8094, or 8120–8124), penis (C600–C609 with any histology), tonsil (C090–C099 with histologies 8050–8076, 8094, or 8120–8124), and conjunctiva (C690 with any histology). We also studied carcinoma *in situ* (behavior code 2) at anogenital sites (cervix, vulva/vagina, anus, and penis) using the same topographic and histologic criteria as for the respective invasive cancers.

Statistical Analysis

Measures of Relative Risk

We used cut points similar to those used in a previous study (3) to divide the time in relation to AIDS onset in the following periods: from 60 to 25 months before AIDS onset (distant pre-AIDS period), from 24 to 7 months before AIDS onset (recent pre-AIDS period), from 6 months before to 3 months after AIDS onset (AIDS period), from 4 to 27 months after AIDS onset (early post-AIDS period), and from 28 to 60 months after AIDS onset (late post-AIDS period). For each period, we calculated estimates of the relative risk (RR) of HPV-associated *in situ* and invasive cancers on the basis of a comparison of observed and expected cancers using methods similar to those described previously (3,4).

Calculation of expected cancers before and at AIDS onset. All individuals who were observed to have cancer in the 5 years prior to AIDS survived long enough after their cancer diagnosis to have developed AIDS. Consequently, estimates of the expected cancers, with which to compare these observed cancers, had to take into account that some patients developed cancer and died or were lost to follow-up before they developed AIDS. To do so, we calculated survival-conditioned cancer incidence rates covering each month up to 5 years before AIDS onset (–1 to –60 months). These rates, covering all 11 regions under study, were divided in strata of sex, race (white, black, or other/unknown), and age (0–4, 5–9, . . . , 80–84, or ≥85 years). Stratum-specific monthly survival-conditioned incidence rates were multiplied by the appropriate person-months of observation among the AIDS patients, and the products were summed to yield the expected number of cancers. To account for changes in cancer survivorship during the years under study, one set of survival-conditioned incidence rates was generated as averages of stratum-specific incidence rates based on cancers diagnosed up to 60 months before January 1, 1987, and January 1, 1988, respectively. This set of rates was used to calculate expected cancers in the pre-AIDS period among patients diagnosed with AIDS in or before 1990. Another set of survival-conditioned incidence rates was generated as averages of stratum-specific incidence rates based on cancers diagnosed up to 60 months before January 1, 1993, and January 1, 1994, respectively. This set of rates was used to calculate expected cancers in the pre-AIDS period among patients diagnosed with AIDS after 1990. Averaged stratum-specific rates were used to stabilize the rates. For a typical month such as –30 months (i.e., 30 months before AIDS onset), the numerator of the survival-conditioned incidence rate comprised 1) all cancer patients diagnosed in that month who were known to be alive 30 months later and 2) the estimated alive fraction of patients diagnosed in that month for whom vital status 30 months later was unknown. To obtain the latter, we applied site-specific national cancer survival data (9) to the group of cancer patients who had unknown vital status 30 months later. This was repeated for every month from –1 to –60 months.

Calculation of expected cancers after AIDS onset. For the post-AIDS periods, we generated sex-specific, race-specific (white, black, or other/unknown), age-specific (0–4, 5–9, . . . , 80–84, or ≥85 years), and period-specific (1978–1982, 1983–1987, 1988–1992, or 1993–1996) incidence rates covering all 11 regions under study. Expected numbers of cancer were calculated as the sum of stratum-specific products of background cancer incidence and person-months at risk among the AIDS patients.

We calculated 95% confidence intervals (CIs) for the RR estimates assuming a Poisson distribution of the observed cancers (10). To provide an overall RR for the cancers studied among patients with AIDS, we used the sum of the observed cancers over the sum of the expected cancers for the 7.25-year period from 60

months before to 27 months after AIDS. For invasive cervical cancer, however, we used the RR for the early post-AIDS period as the overall RR measure, since, by definition, no case of invasive cervical cancer occurred before AIDS.

RRs for HPV-associated cancers were calculated for groups of patients defined by age at AIDS (<30, 30–39, 40–49, or ≥50 years), by ethnic group (white, black, Hispanic, or other/unknown, as categorized in the AIDS registries), and by HIV-exposure group (homosexual contact [men only, including homosexual intravenous drug users], heterosexual contact, nonhomosexual intravenous drug users, patients infected during treatment of hemophilia or other bleeding disorders or via transfusion or transplantation, or other/unknown HIV exposure). For all estimates of the RR, expected cancers among patients categorized in AIDS registries as Hispanics were derived from cancer rates for whites because cancer registries do not provide cancer rates specific to Hispanics.

Malignancies may occur in excess among AIDS patients for reasons that are not related to HIV or HIV-mediated cellular immunosuppression. To address this issue, we expanded previously defined criteria (3) to distinguish cancers that are likely to be influenced by reduced cellular immunity from those that are not. Specifically, a cancer was considered to be potentially influenced by HIV-mediated immunosuppression when three criteria were all met: 1) The overall RR for the period from 60 months before to 27 months after AIDS had to be statistically significantly elevated (cancers occurring in the late post-AIDS period were not included in this overall RR measure because of increasing uncertainty about the number of patients at risk with time since AIDS onset); 2) the RR in the early post-AIDS period had to be statistically significantly elevated; and 3) there had to be a statistically significant increasing trend in the RRs from the pre-AIDS period to the post-AIDS period (excluding the AIDS period to minimize ascertainment bias). To evaluate the trend, we applied a score test of $\beta = 0$ in a Poisson regression model with expectation $(E)\exp(\alpha + \beta t)$. In this model, E was the expected cancer count based on incidence rates in the underlying population, and α was the sum of the observed cancers divided by the sum of the expected cancers for the periods contributing information to the trend test. When numbers of observed cancers were sufficient (minimum, 25), we used information from the distant and recent pre-AIDS periods and the early post-AIDS period, using mid-points for these intervals ($t = -42.5$, -15.5 , and 15.5 months, respectively) as values of t . For cancers with fewer than 25 observed cases, we included data from the late post-AIDS period (with the corresponding mid-point, $t = 44$ months) in the trend test to use the maximum information available. Since underascertainment of deaths and migration out of the catchment areas among AIDS patients renders the person-time at risk in the late post-AIDS period too high, and thus the corresponding RR too low, the trend test for the less common cancers is likely to be conservative. When 95% CIs excluded unity and two-sided P values for trend were less than .05, we considered RRs and trends to be statistically significant.

For the subgroup of patients with CD4⁺ T-lymphocyte counts available in AIDS registries, we also evaluated the impact of CD4⁺ levels at the time of AIDS onset on the cancer risk in the post-AIDS period. Specifically, analyses of the RR in the early post-AIDS period were done in strata of CD4⁺ counts per μL (<100, 100–199, and ≥200 μL) at the time from 1 month before to 1 month after the onset of AIDS.

We performed a sensitivity analysis to evaluate the robustness of our findings for the anogenital HPV-associated cancers based on the criteria mentioned above. In this analysis, we divided the time relative to AIDS onset in three new pre-AIDS periods (60–41 months before AIDS onset [with mid-point, $t = -50.5$ months], 40–21 months before AIDS onset [$t = -30.5$ months], and 20–7 months before AIDS onset [$t = -13.5$ months]), the AIDS period (6 months before to 3 months after AIDS onset [period not included in trend tests]), and two new post-AIDS periods (4–24 months after AIDS onset [$t = 14$ months] and 25–60 months after AIDS onset [$t = 42.5$ months]). With these alternative time intervals, we used criteria similar to those mentioned above to identify cancers potentially influenced by immunosuppression: 1) The overall RR had to be statistically significantly elevated (now based on the period from 60 months before AIDS onset to 24 months after AIDS onset); 2) the RR for the early post-AIDS period had to be statistically significantly elevated (now from 4 to 24 months after AIDS onset); and 3) there had to be a statistically significant increasing trend in the RR from the pre-AIDS to the post-AIDS period based on the four periods, with $t = -50.5$, -30.5 , -13.5 , and 14 months (five periods with $t = -50.5$, -30.5 , -13.5 , 14, and 42.5 months, when there were <25 observed cancers).

Finally, we evaluated the potential impact of ascertainment and reporting biases on our findings for the HPV-associated *in situ* cancers. *In situ* lesions may

be underreported in cancer registries and could thus be artificially increased in the post-AIDS period because of more extensive diagnostic activity during clinical follow-up. To address this issue, we did supplementary RR and trend analyses for the group of all *in situ* cancers at anatomic sites other than the cervix, vulva/vagina, anus, and penis.

RESULTS

Overall, we identified 366 034 patients who were diagnosed with AIDS during the linkage period. We excluded 56 669 patients (15.5%) whose initial AIDS diagnoses occurred outside the interval when corresponding AIDS and cancer registries were considered complete (Table 1). The patients excluded and those included in the study (total, 309 365; 257 605 males and 51 760 females) were similar in proportion with respect to sex, age, ethnic group, and route of HIV acquisition (data not shown). The two geographic areas contributing most of the AIDS patients to the study were New York and Florida, with 48% of the male patients and 60% of the female patients (Table 1). End points for follow-up after AIDS onset were death ($n = 189\,915$; 61.4%), censoring at 60 months after AIDS onset ($n = 17\,252$; 5.6%), or last date with complete cancer data in the cancer registry ($n = 102\,198$; 33.0%).

Demographic characteristics and route of HIV acquisition for the 309 365 AIDS patients are shown in Table 2. Among both males and females, the majority of patients (88% and 86%, respectively) were between 20 and 49 years old at AIDS onset. Almost one half (48%) of the male patients were whites, whereas blacks were the predominant ethnic group (57%) among women. Homosexual men (including homosexual intravenous drug users) constituted 62% of the men in the study followed by 26% nonhomosexual intravenous drug users and 3% who were HIV infected through heterosexual contact. Among women, 47% were infected through intravenous drug use, and 34% were infected heterosexually (Table 2).

Among the HIV/AIDS patients, a total of 1586 cases (1154 in women and 432 in men) of HPV-associated cancer (including carcinoma *in situ* of the cervix, anus, vulva/vagina, and penis) occurred in the interval from 60 months before to 60 months after AIDS (Table 1). The majority of these were cervical carcinomas (767 *in situ* and 355 invasive), of which 296 invasive cervical cancers were AIDS-defining events in HIV-infected women (Table 3).

Anogenital HPV-Associated Cancers

During the period from 60 months before to 27 months after AIDS onset, overall risks of HPV-associated cancers were statistically significantly elevated at all anogenital sites studied (Table 4). The level of increase, however, varied by anatomic site, age group, ethnic group, HIV exposure category, and level of immunosuppression.

Risks by Age and Ethnic Group

Cervical cancer. Invasive cervical cancer occurred in statistically significant excess among women with AIDS. In the early post-AIDS period, 44 cases occurred versus 8.2 expected (RR = 5.4; 95% CI = 3.9–7.2), and the risk remained high in the 28–60-month post-AIDS period (RR = 5.1; 95% CI = 2.9–8.5; $n = 15$). Age did not influence the RR (Table 4). Hispanic women were at high risk (RR = 8.5; 95% CI = 4.5–14.5) (Table 5). The overall RR for *in situ* cervical cancer (RR = 4.6;

Table 2. Demographic characteristics and route of HIV transmission among 309 365 patients with AIDS (AIDS–Cancer Match Registry, United States, 1978–1996)*

Characteristic	Men	Women
Age at AIDS onset, y		
<20	3114 (1.2%)	2820 (5.4%)
20–29	38 493 (14.9%)	10 826 (20.9%)
30–39	116 987 (45.4%)	23 532 (45.5%)
40–49	70 252 (27.3%)	10 334 (20.0%)
50–59	21 403 (8.3%)	2776 (5.4%)
60–69	6187 (2.4%)	1064 (2.1%)
70–79	1060 (0.4%)	354 (0.7%)
≥80	109 (0.0%)	54 (0.1%)
All ages	257 605 (100%)	51 760 (100%)
Median age in y (range)	37 (0–99)	34 (0–90)
Median year of onset (range)	1991 (1978–1996)	1992 (1979–1996)
Ethnic group		
White	122 524 (47.6%)	11 046 (21.3%)
Black	82 375 (32.0%)	29 660 (57.3%)
Hispanic	49 904 (19.4%)	10 693 (20.7%)
Other/unknown	2802 (1.1%)	361 (0.7%)
Route of HIV acquisition		
Homosexual contact	144 022 (55.9%)	—
Homosexual contact + intravenous drug use	15 685 (6.1%)	—
Heterosexual contact		
With unspecified partner of opposite sex	7909 (3.1%)	7356 (14.2%)
With bisexual male partner	—	1259 (2.4%)
With nonbisexual male partner	—	8770 (16.9%)
Intravenous drug use	67 184 (26.1%)	24 276 (46.9%)
Transfusion or transplantation	2066 (0.8%)	1628 (3.1%)
Hemophilia or other bleeding disorders	1509 (0.6%)	111 (0.2%)
Vertical transmission	2225 (0.9%)	2256 (4.4%)
Unknown	17 005 (6.6%)	6104 (11.8%)

*HIV = human immunodeficiency virus; AIDS = acquired immunodeficiency syndrome.

95% CI = 4.3–5.0) showed no particular pattern with age (Table 4) or ethnic group (Table 5).

Vulvar/vaginal cancer. For both invasive and *in situ* cancers of the vulva/vagina, RRs were high (Table 4). In the age group 0–29 years, RRs were 37.2 (95% CI = 7.7–108.8) for invasive lesions and 14.5 (95% CI = 4.0–37.1) for *in situ* lesions. Hispanic women appeared to be at higher risk for invasive but at lower risk for *in situ* vulvar/vaginal cancer than were whites and blacks (Table 5).

Anal cancer. Invasive and *in situ* anal cancers occurred in a remarkable excess, particularly among patients under age 30 years, among whom RRs were above 100 (Table 4). Among older men, the risk was significantly increased at 20- to 40-fold above background. Among women, RRs for invasive anal cancer (RR = 6.8; 95% CI = 2.7–14.0) and *in situ* anal cancer (RR = 7.8; 95% CI = 0.2–43.6) were as high as those for cervical and vulvar/vaginal cancers. Although elevated in all ethnic groups, RRs for anal cancer were higher in whites than in blacks or Hispanics (Table 5).

Penile cancer. Like anal and vulvar/vaginal cancers, invasive penile cancer (RR = 37.2; 95% CI = 7.7–108.6) and *in situ* penile cancer (RR = 16.1; 95% CI = 4.4–41.2) occurred in particular excess among those aged 0–29 years (Table 4). Considering all age groups together, risks of both invasive and *in situ* penile cancers were increased fivefold or more among blacks and Hispanics, whereas RRs were lower and not statistically significantly elevated among whites (Table 5).

Risks by HIV Exposure Group

RRs for the invasive and *in situ* cancers were similar among intravenous drug-using and heterosexually infected women

(Table 6). In the small group of women who acquired HIV during treatment of bleeding disorders or via blood transfusion or transplantation, no case of invasive HPV-associated anogenital cancer occurred versus 0.51 expected. However, the RR of *in situ* cervical cancer was nearly as high in these women as in other HIV exposure categories (RR = 3.9; 95% CI = 2.1–6.5).

Among men who were HIV infected through homosexual contact, anal cancer occurred in extreme excess (for invasive anal cancer [RR = 59.5; 95% CI = 51.5–68.4]; for *in situ* anal cancer [RR = 99.8; 95% CI = 81.4–121.2]), but intravenous drug users and those with an undetermined route of HIV transmission were also at increased anal cancer risk. Risk of invasive penile cancer was increased 7.1-fold among intravenous drug users, whereas it appeared less marked (RR = 2.8; 95% CI = 1.0–6.1) among homosexual men. There was no apparent difference by exposure group for *in situ* penile cancers (Table 6).

Risks in Relation to Onset of AIDS

All four types of invasive anogenital cancer were significantly elevated in the early post-AIDS period (Fig. 1). Since, by definition, invasive cervical cancer could not occur in the pre-AIDS period, no trend test was performed for this cancer. RRs did not increase over time for invasive cancers of the vulva/vagina (*P* for trend = .84) or anus (*P* for trend = .96 among men; *P* for trend = .66 among women). However, RRs for invasive penile cancer did increase significantly from the pre-AIDS to the post-AIDS period (*P* for trend = .04).

Like their invasive counterparts, *in situ* cancers at all anogenital sites occurred in statistically significant excess in the early post-AIDS period. However, RRs increased significantly

Table 3. Age distribution and post-AIDS incidence of human papillomavirus-associated cancers among 309 365 patients with AIDS (AIDS–Cancer Match Registry, United States, 1978–1996)

Cancer site	No. of patients*	Mean age at cancer, y (range)	<i>In situ</i> /invasive, mean age difference for AIDS patients versus all patients, y†	Incidence per 100 000 person-years‡
Cervix				
Invasive	355	35.9 (17–67)	3.2 versus 15.7	85.7
<i>In situ</i>	767	32.7 (13–61)		337.4
Vulva/vagina				
Invasive	13	33.0 (23–59)	–2.8 versus 16.2	7.9
<i>In situ</i>	11	35.8 (24–54)		8.2
Anus§				
Invasive	239	40.9 (21–66)	3.9 versus 13.1	18.2 (men) 3.9 (women)
<i>In situ</i>	121	37.0 (20–57)		12.3 (men) —¶ (women)
Penis				
Invasive	16	41.0 (25–67)	1.7 versus 7.6	1.9
<i>In situ</i>	25	39.3 (21–67)		2.8
Tonsil, invasive				
Women	0	—	NA#	—
Men	32	50.3 (39–79)		3.0
Conjunctiva, invasive				
Women	0	—	NA#	—
Men	7	45.0 (29–61)		0.4

*Number of patients with cancer from 60 months before to 60 months after acquired immunodeficiency syndrome (AIDS).

†Differences between mean age at *in situ* and invasive cancers for all patients are based on age distributions for all patients in the numerators of the underlying incidence rates for the 11 areas under study.

‡Crude incidence in 2-year period 4–27 months after AIDS.

§Men and women combined (includes seven women with invasive anal cancer [mean age, 37.0 years] and one with *in situ* anal cancer [age, 27 years]).

||Incidence rates of invasive anal cancer and *in situ* anal cancer among men who were human immunodeficiency virus infected through homosexual contact were 23.9 and 18.2 per 100 000 person-years, respectively.

¶No case of *in situ* anal cancer in the period from 4 to 27 months after AIDS among women.

#NA = not analyzed.

Table 4. Relative risks* (by age at onset of acquired immunodeficiency syndrome [AIDS]) of human papillomavirus-associated anogenital cancers among 309 365 patients with AIDS (AIDS–Cancer Match Registry, United States, 1978–1996)

Age at AIDS onset, y	Relative risk (95% confidence interval) [No. of observed cancers]									
	Cervix		Vulva/vagina		Anus (women)		Anus (men)		Penis	
<i>Invasive cancers</i>										
<30	6.1 (2.6–12.0)	[8]	37.2 (7.7–108.8)	[3]	134.3 (16.3–484.8)	[2]	162.7 (103.1–244.0)	[23]	37.2 (7.7–108.6)	[3]
30–39	5.9 (3.8–8.7)	[24]	8.5 (3.1–18.4)	[6]	12.2 (2.5–35.7)	[3]	40.1 (31.2–50.8)	[69]	7.4 (2.4–17.3)	[5]
40–49	6.0 (3.1–10.4)	[12]	3.0 (0.4–10.8)	[2]	2.8 (0.1–15.6)	[1]	39.3 (31.3–48.7)	[83]	2.2 (0.4–6.3)	[3]
≥50	—†	[0]	1.7 (0.0–9.3)	[1]	2.4 (0.1–13.5)	[1]	23.4 (16.6–32.0)	[39]	1.8 (0.4–5.3)	[3]
All	5.4 (3.9–7.2)	[44]	5.8 (3.0–10.2)	[12]	6.8 (2.7–14.0)	[7]	37.9 (33.0–43.4)	[214]	3.7 (2.0–6.2)	[14]
<i>In situ cancers</i>										
<30	5.3 (4.6–6.1)	[203]	14.5 (4.0–37.1)	[4]	—		130.4 (71.2–219.0)	[14]	16.1 (4.4–41.2)	[4]
30–39	4.3 (3.9–4.8)	[388]	3.4 (0.9–8.7)	[4]	21.0 (0.5–117.1)	[1]	72.7 (55.5–93.6)	[60]	8.4 (3.6–16.5)	[8]
40–49	4.7 (3.9–5.7)	[114]	1.0 (0.0–5.8)	[1]	—		38.0 (24.3–56.2)	[24]	4.8 (1.3–12.4)	[4]
≥50	4.1 (2.4–6.6)	[17]	5.1 (0.6–18.5)	[2]	—		40.2 (17.3–79.3)	[8]	4.6 (1.3–11.8)	[4]
All	4.6 (4.3–5.0)	[722]	3.9 (2.0–7.0)	[11]	7.8 (0.2–43.6)	[1]	60.1 (49.2–72.7)	[106]	6.9 (4.2–10.6)	[20]

*For all cancers, except invasive cervical cancer, the relative risk is the ratio of observed-to-expected cancers for the period 60 months before to 27 months after AIDS. The relative risk for invasive cervical cancer pertains to the period from 4 to 27 months after AIDS.

†Number of expected invasive cervical cancers among women aged ≥50 years = 0.74.

from the pre-AIDS to the post-AIDS period for *in situ* lesions of the cervix (P for trend < .001), vulva/vagina (P for trend = .04), and penis (P for trend = .04) (Fig. 1).

Risks in Relation to CD4⁺ Level

Thirty percent of the patients (77 054 males and 16 150 females) had a CD4⁺ T-lymphocyte count within ±1 month of

AIDS onset. The age composition among these subjects was similar to that of the entire population of the AIDS patients shown in Table 2. However, among patients with CD4⁺ counts, there were proportionally fewer Hispanics (17.7% of the men and 16.4% of the women) and nonhomosexual intravenous drug users (20.8% of the men and 37.9% of the women) and proportionally more patients who were HIV infected heterosexually with an unspecified partner (22.2% of the women) or by an

Table 5. Relative risks* (by ethnic group) of human papillomavirus-associated anogenital cancers among 309 365 patients with acquired immunodeficiency syndrome (AIDS) (AIDS–Cancer Match Registry, United States, 1978–1996)

Ethnic group	Relative risk (95% confidence interval) [No. of observed cancers]									
	Cervix		Vulva/vagina		Anus (women)		Anus (men)		Penis	
<i>Invasive cancers</i>										
White	6.8 (3.5–11.8)	[12]	2.0 (0.1–11.4)	[1]	15.0 (4.1–38.5)	[4]	54.7 (46.1–64.4)	[143]	1.8 (0.4–5.2)	[3]
Black	4.0 (2.4–6.2)	[19]	4.3 (1.4–9.9)	[5]	3.6 (0.4–13.0)	[2]	22.3 (16.3–29.7)	[46]	5.3 (2.3–10.4)	[8]
Hispanic	8.5 (4.5–14.5)	[13]	15.5 (5.7–33.7)	[6]	4.8 (0.1–27.0)	[1]	21.5 (13.1–33.1)	[20]	5.4 (1.1–15.6)	[3]
Other/unknown	—	[0]	—	[0]	—	[0]	156.3 (50.7–364.2)	[5]	—	[0]
All	5.4 (3.9–7.2)	[44]	5.8 (3.0–10.2)	[12]	6.8 (2.7–14.0)	[7]	37.9 (33.0–43.4)	[214]	3.7 (2.0–6.2)	[14]
<i>In situ cancers</i>										
White	4.9 (4.2–5.6)	[185]	5.5 (1.5–14.1)	[4]	29.8 (0.8–165.8)	[1]	109.7 (87.6–135.6)	[85]	2.8 (0.8–7.1)	[4]
Black	4.5 (4.1–5.0)	[356]	4.4 (1.6–9.6)	[6]	—	[0]	19.8 (10.5–33.9)	[13]	8.8 (3.5–18.1)	[7]
Hispanic	4.7 (4.0–5.4)	[176]	1.4 (0.0–8.0)	[1]	—	[0]	22.1 (8.9–45.5)	[7]	16.2 (7.4–30.7)	[9]
Other/unknown	2.9 (1.0–6.8)	[5]	—	[0]	—	[0]	69.4 (1.8–386.7)	[1]	—	[0]
All	4.6 (4.3–5.0)	[722]	3.9 (2.0–7.0)	[11]	7.8 (0.2–43.6)	[1]	60.1 (49.2–72.7)	[106]	6.9 (4.2–10.6)	[20]

*For all cancers, except invasive cervical cancer, the relative risk is the ratio of observed-to-expected cancers for the period 60 months before to 27 months after AIDS. The relative risk for invasive cervical cancer pertains to the period from 4 to 27 months after AIDS.

Table 6. Relative risks* (by human immunodeficiency virus [HIV] exposure group) of human papillomavirus-associated anogenital cancers among 309 365 patients with acquired immunodeficiency syndrome (AIDS) (AIDS–Cancer Match Registry, United States, 1978–1996)

	Relative risk (95% confidence interval) [No. of observed cancers]									
HIV exposure category	Cervix		Vulva/vagina		Anus (women)		Anus (men)		Penis	
	<i>Invasive cancers</i>									
Homosexual contact†	NA‡		NA‡		NA‡		59.5 (51.5–68.4)	[197]	2.8 (1.0–6.1)	[6]
Heterosexual contact	4.9 (2.7–8.2)	[14]	7.1 (2.3–16.4)	[5]	8.0 (1.7–23.4)	[3]	—	[0]	—	[0]
Intravenous drug use§	7.0 (4.7–10.0)	[29]	5.5 (1.8–12.8)	[5]	7.3 (1.5–21.4)	[3]	5.9 (2.7–11.2)	[9]	7.1 (2.8–14.6)	[7]
Hemophilia/transfusion	—	[0]	—	[0]	—	[0]	—	[0]	—	[0]
Other/unknown¶	1.1 (0.0–6.2)	[1]	7.0 (0.9–25.3)	[2]	6.4 (0.2–35.9)	[1]	17.1 (7.4–33.7)	[8]	2.7 (0.1–15.1)	[1]
All	5.4 (3.9–7.2)	[44]	5.8 (3.0–10.2)	[12]	6.8 (2.7–14.0)	[7]	37.9 (33.0–43.4)	[214]	3.7 (2.0–6.2)	[14]
	<i>In situ cancers</i>									
Homosexual contact†	NA‡		NA‡		NA‡		99.8 (81.4–121.2)	[102]	6.1 (3.0–10.9)	[11]
Heterosexual contact	4.5 (4.0–5.1)	[251]	5.1 (1.7–12.0)	[5]	—	[0]	—	[0]	9.5 (0.2–52.8)	[1]
Intravenous drug use§	4.6 (4.2–5.1)	[371]	2.2 (0.5–6.3)	[3]	17.2 (0.4–96.0)	[1]	5.6 (1.2–16.5)	[3]	7.2 (2.3–16.8)	[5]
Hemophilia/transfusion	3.9 (2.1–6.5)	[14]	—	[0]	—	[0]	—	[0]	15.8 (0.4–87.9)	[1]
Other/unknown¶	5.0 (4.0–6.2)	[86]	9.0 (1.9–26.3)	[3]	—	[0]	7.9 (0.2–43.7)	[1]	9.0 (1.1–32.4)	[2]
All	4.6 (4.3–5.0)	[722]	3.9 (2.0–7.0)	[11]	7.8 (0.2–43.6)	[1]	60.1 (49.2–72.7)	[106]	6.9 (4.2–10.6)	[20]

*For all cancers, except invasive cervical cancer, the relative risk is the ratio of observed-to-expected cancers for the period 60 months before to 27 months after AIDS. The relative risk for invasive cervical cancer pertains to the period from 4 to 27 months after AIDS.

†Men only. Includes homosexual men who use intravenous drugs.

‡NA = not applicable.

§Excludes homosexual men who use intravenous drugs.

||Includes patients who were HIV infected during treatment for hemophilia or other bleeding disorders or via transfusion or organ transplantation.

¶Includes patients who were HIV infected through vertical transmission.

unknown route (8.4% of the men and 16.5% of the women). Overall, the mean CD4⁺ count at AIDS onset (within ± 1 month) was 111.5/ μ L (interquartile range, 33–170/ μ L) in males and 109.5/ μ L (interquartile range, 30–168/ μ L) in females.

We evaluated the impact of CD4⁺ levels at AIDS onset on the risk of developing cervical cancer among women and anal cancer among men in the early post-AIDS period. For comparison, we also calculated RRs according to CD4⁺ levels at AIDS onset for Kaposi's sarcoma (based on 1844 cases) and non-Hodgkin's lymphoma (based on 1084 cases). The post-AIDS RRs for both Kaposi's sarcoma and non-Hodgkin's lymphoma increased with decreasing CD4⁺ counts, with patients having CD4⁺ counts less than 100/ μ L (median, 33/ μ L) at more than twice the RR of patients with CD4⁺ counts of greater than or equal to 200 μ L

(median, 270/ μ L) (Fig. 2). However, based on 99 cervical cancers (23 invasive and 76 *in situ*) and 38 anal cancers in men (21 invasive and 17 *in situ*), RRs for these malignancies did not show increasing patterns with decreasing CD4⁺ counts. Further subdivision of CD4⁺ counts (<20, 20–49, 50–99, 100–149, 150–199, and ≥ 200 CD4⁺ T lymphocytes per μ L) did not reveal any association for cervical or anal malignancies with extreme levels of immunosuppression (data not shown).

Other HPV-Associated Cancers

While no cases of tonsillar (versus 0.59 expected) or conjunctival (versus 0.04 expected) cancers were diagnosed in HIV-infected women in the period from 60 months before to 27 months after AIDS, both cancers occurred in statistically sig-

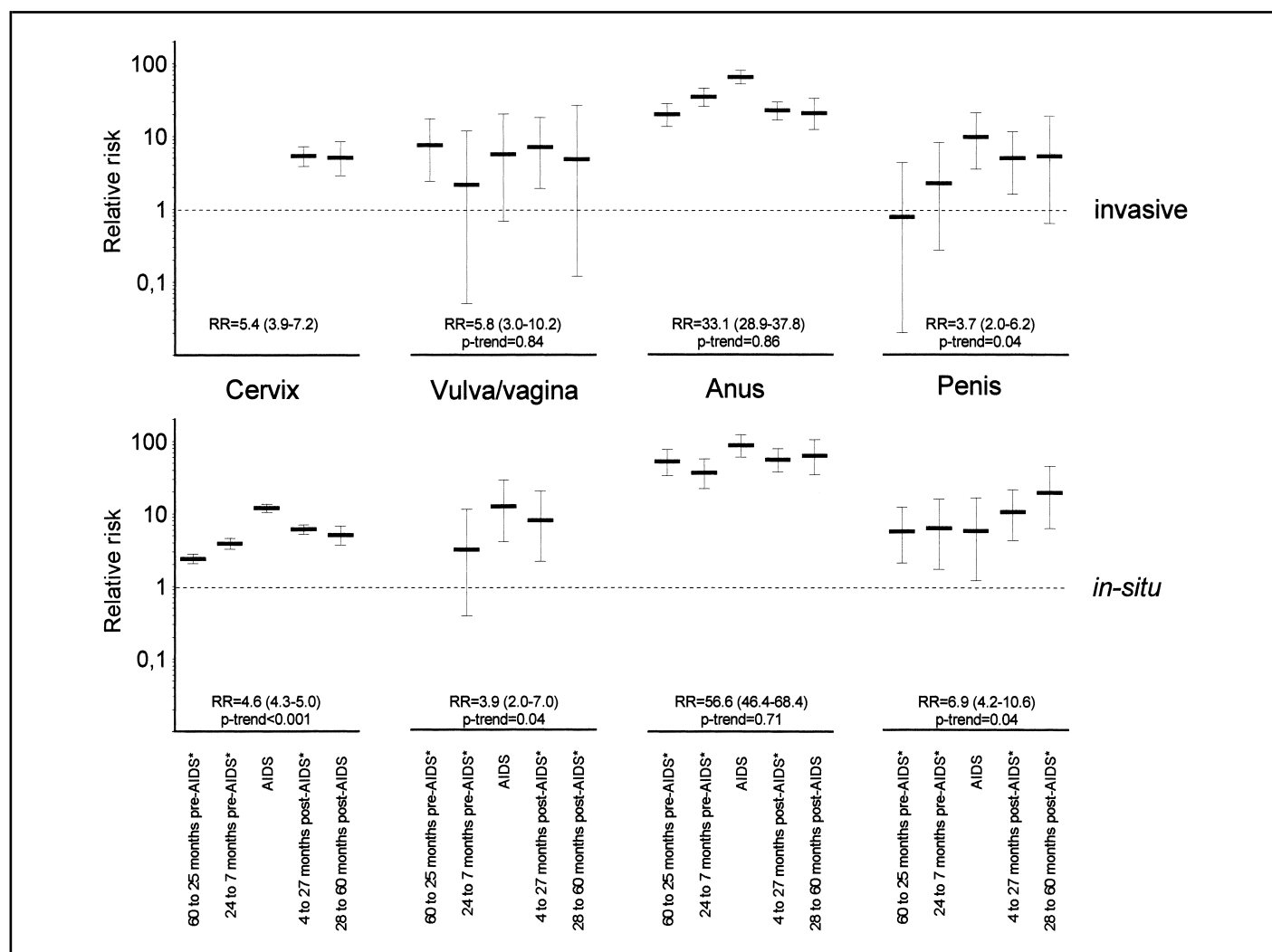


Fig. 1. Relative risks (RRs) of invasive and *in situ* anogenital human papillomavirus-associated carcinomas in patients with human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) in relation to time of AIDS onset. Except for invasive cervical cancer, RRs on the bottom panel indicate the overall RR estimate (95% confidence interval) for the

period from 60 months before AIDS onset to 27 months after AIDS onset. For invasive cervical cancer, the RR pertains to the period 4–27 months after AIDS onset. Data for anal cancers are for women and men combined. For each site, the *P* value (two-sided) indicates a test for change in RR over time using the periods indicated with an asterisk.

nificant excess among men. For tonsillar cancer, the overall RR among men was 2.6 (95% CI = 1.8–3.8; *n* = 29). Among white, black, and Hispanic men, the RRs for tonsillar cancer were 2.0 (95% CI = 0.9–3.8; *n* = 9), 3.2 (95% CI = 1.8–5.1; *n* = 16), and 2.6 (95% CI = 0.7–6.7; *n* = 4), respectively. Tonsillar cancer risk appeared high among heterosexually HIV-infected men, but numbers were limited (RR = 5.3; 95% CI = 1.1–15.4; *n* = 3). Seven men developed conjunctival cancer (RR = 14.6; 95% CI = 5.8–30.0), including four whites (RR = 12.7; 95% CI = 3.5–32.6) and three Hispanics (RR = 25.6; 95% CI = 5.3–74.9). Neither tonsillar cancer nor conjunctival cancer risk was increased significantly in the early post-AIDS period, and no statistically significant pre-AIDS to post-AIDS trend was seen (*P* for trend = .35 for tonsillar cancer and *P* for trend = .21 for conjunctival cancer).

Sensitivity Analysis

Our findings for the invasive and *in situ* HPV-associated anogenital cancers were robust with respect to each of the three criteria used to identify potentially immunosuppression-associated

malignancies. Overall, RR estimates based on the period from 60 months before to 24 months after AIDS onset remained virtually unchanged compared with the RRs for the period from 60 months before to 27 months after AIDS onset (<3% difference at all sites), and all new overall RR estimates were statistically significantly above unity. Also, RR estimates for the new post-AIDS period from 4 to 24 months after AIDS onset were rather close to RRs for the period from 4 to 27 months after AIDS onset (<9% difference at all sites), and all new RR estimates remained statistically significantly elevated. Finally, statistically significant increasing trends for HPV-associated *in situ* cancers also had *P* values of less than .05 in the new trend analyses. The only difference between the two analyses was that the trend for invasive penile cancer became statistically insignificant (*P* for trend = .07) in the new analysis.

In Situ Cancers at Nonanogenital Sites

A total of 107 carcinomas *in situ* at sites other than the cervix, vulva/vagina, anus, and penis (83 in males and 24 in females) were recorded in cancer registries from 60 months before to 27

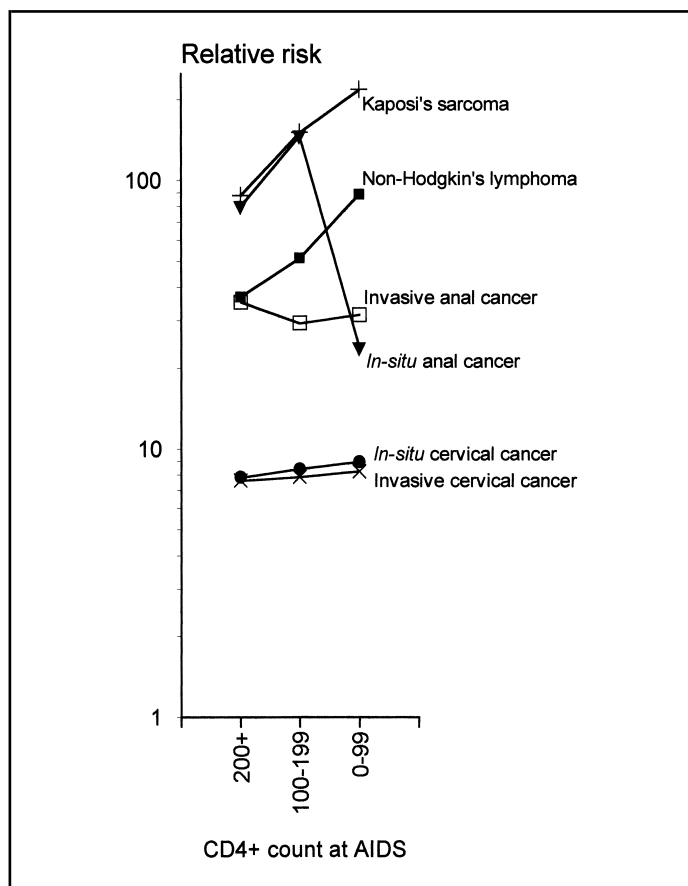


Fig. 2. Relative risks (RRs) of developing cervical cancer (invasive or *in situ*), anal cancer (invasive or *in situ*, males only), Kaposi's sarcoma, or non-Hodgkin's lymphoma in the 4–27 months after the acquired immunodeficiency syndrome (AIDS) period, according to the CD4⁺ T-lymphocyte count within ± 1 month of AIDS onset. For CD4⁺ counts at the time of AIDS of greater than or equal to 200/ μ L, 100–199/ μ L, and 0–99/ μ L, respectively, the RRs were as follows: invasive cervical cancer—7.5 (95% confidence interval [CI] = 0.9–27.2), 7.7 (95% CI = 3.9–13.8), and 7.9 (95% CI = 3.8–14.5); *in situ* cervical cancer—7.8 (95% CI = 2.8–16.9), 8.3 (95% CI = 5.8–11.5), and 8.6 (95% CI = 5.9–12.0); invasive anal cancer, males only—34.9 (95% CI = 7.2–101.8), 28.9 (95% CI = 13.2–54.9), and 30.0 (95% CI = 13.7–57.0); *in situ* anal cancer, males only—79.6 (95% CI = 9.6–287.5), 144.4 (95% CI = 76.8–246.9), and 22.7 (95% CI = 2.7–81.8); Kaposi's sarcoma—87.2 (95% CI = 72.2–104.4), 148.4 (95% CI = 137.8–159.5), and 207.3 (95% CI = 194.6–220.6); and non-Hodgkin's lymphoma—36.6 (95% CI = 28.8–45.8), 50.4 (95% CI = 45.6–55.7), and 84.7 (95% CI = 78.1–91.6).

months after AIDS onset. The overall risk for these lesions was slightly increased (overall RR = 1.5; 95% CI = 1.2–1.8), mainly because of a high risk (RR = 3.0; 95% CI = 2.1–4.1; $n = 35$) in the AIDS period. However, there was no excess in the early post-AIDS period (RR = 1.0; 95% CI = 0.6–1.6; $n = 18$), and there was no suggestion of an increasing trend from pre-AIDS to post-AIDS (P for trend = .28).

DISCUSSION

On the basis of the largest population-based dataset available for the study of cancer in immunosuppressed individuals, our study shows that, compared with the general population, HIV-infected individuals are at considerably increased risk for all types of anogenital HPV-associated cancers and for their *in situ* precursor lesions. This risk elevation spans the decade from 5 years before to 5 years after AIDS. Although these observa-

tions are of greater breadth and depth than those of previous reports, our findings are not surprising. The major transmission route for both HPV and HIV is unprotected sexual contact with an infected partner. In addition, HIV-infected people are more likely to have detectable anogenital HPV infection than are HIV-uninfected people in comparable risk groups (11–16), probably because HPV viral load is inversely related to the level of cellular immune competence (12,15,17). Consequently, our finding of a high incidence of all the invasive and *in situ* anogenital cancers studied is explained partly by shared routes of viral transmission and persistence of HPV. In addition, persons at risk of HIV and of other sexually transmitted diseases may have lifestyles involving more exposure to other potential cofactors in HPV-induced carcinogenesis, such as tobacco smoking (18,19).

Cross-sectional studies (20–26) have shown an increased prevalence of SILs of the cervix, vulva, and anus in HIV-infected individuals. Also, invasive cervical cancer in women and invasive anal cancer in men occurred excessively among HIV-infected individuals (3,4,27). Our findings lend strong support to these observations. We also add invasive vulvar/vaginal cancer, invasive anal cancer in women, and both *in situ* and invasive cancers of the penis to the list of lesions occurring at significantly increased frequency with HIV.

Mucosotropic types of HPV, mainly HPV16 and HPV18, are involved in most invasive and *in situ* cancers of the cervix and anal canal (28,29) and in a considerable proportion of vulvar/vaginal and penile cancers (30,31). The higher risk of persistent HPV infection among HIV-infected subjects probably reflects an impaired ability to clear HPV in the HIV-immunocompromised host (32,33). Accordingly, HPVs may cause relatively undisturbed epithelial proliferation in HIV-infected individuals, resulting in the gradual and perhaps hastened progression from infection or reactivation through low-grade to high-grade SILs (34–37). It has been suggested that impaired cytotoxic T-lymphocyte reactivity to HPV oncoproteins E6 and E7 in HIV-infected individuals may explain this progression (38). An alternative, but not mutually exclusive, hypothesis is that systemic HIV infection alters cytokine expression in epithelial cells, which, in turn, increases the susceptibility for HPV infection or alters the course of already established HPV infection. A direct action of HIV proteins on HPV-infected epithelial cells has also been suggested, but supporting data are sparse. If occurring at all, co-localization of HIV and HPV in keratinocytes is not common (13,39).

HPVs may be necessary for the development of anogenital high-grade SILs, but they are not believed to be responsible for the final genetic changes leading to invasion (40). In the general population, patients with *in situ* anogenital cancers are, on average, 7.6–16.2 years younger than those with invasive cancers, depending on the site (Table 3). Among HIV/AIDS patients with such malignancies, the corresponding age differences were considerably lower (–2.8 to 3.9 years), depending on the site. Although these intervals should be compared cautiously because of differences in the underlying age distributions, the short time interval between *in situ* and invasive cancers and the young age at which invasive anogenital cancers occur in patients with AIDS suggest two possible mechanisms. One is the faster accrual of additional genetic damage in rapidly proliferating cells whose ability to induce cell cycle arrest or undergo apoptosis is hampered by HPV-E6-mediated degradation of p53 (41). Alternatively, as yet unknown, late-stage cofactors involved in the

final step from *in situ* to invasive cancer might be present in a considerable proportion of HIV-infected individuals.

We required three criteria to be met for a cancer to be considered potentially influenced by immunosuppression. These included 1) a statistically significantly elevated overall RR, 2) a statistically significantly elevated RR in the early post-AIDS period, and 3) a statistically significant increase in RR from the pre-AIDS to the post-AIDS period. According to these criteria, and with the use of two sets of cut points for the AIDS-relative time, *in situ* cancers of the uterine cervix, vulva/vagina, and penis showed patterns compatible with a role for immunosuppression. However, we found little evidence that immunosuppression plays a role beyond the stage of carcinoma *in situ*. Of invasive cancers, only penile cancer met the criterion of increasing RRs in relation to onset of AIDS, but the sensitivity analysis showed that this penile cancer finding was not robust.

The increasing trends for *in situ* cancers and, possibly, invasive penile cancer could be influenced, to some extent, by a combination of incomplete registration and better medical attention after than before the AIDS diagnosis. The majority of women studied were from socially underprivileged groups, including blacks, Hispanics, and intravenous drug users, who are likely to be medically underserved. Among men, both invasive and *in situ* penile cancers occurred in excess, particularly among blacks and Hispanics, who also are circumcised less often than are whites (42). In contrast, *in situ* and invasive anal cancer, which occurred predominantly in homosexual white men, did not increase from the pre-AIDS to the post-AIDS period. A combination of better access to health care and a greater alertness to signs and symptoms of anal disease may explain the high and rather constantly elevated risks of precancerous and invasive anal lesions in this group. However, our analysis for nonanogenital *in situ* cancers showed no excess in the post-AIDS period, and there was no statistically significant trend between pre-AIDS to post-AIDS periods for these lesions. Consequently, our findings for the HPV-associated anogenital *in situ* cancers are likely to reflect a genuine association with immunosuppression.

The increasing trends for HPV-associated anogenital *in situ* cancers are compatible with cross-sectional studies showing increasing risks of anogenital SILs with declining CD4⁺ counts (43). Also, prospective cohort studies (15,17,19,33,36,44,45) have addressed the impact of HIV-related immunodeficiency on the risk of anogenital neoplasia. For anal SILs among homosexual men, which have been investigated in most detail, two studies (15,17) reported incidence rates of anal high-grade SILs that were approximately three times higher among HIV-positive than among HIV-negative homosexual men. Moreover, after adjustment for HPV status, HIV-positive men with CD4⁺ counts less than or equal to 500/ μ L at baseline were at higher risk than those with CD4⁺ counts above 500/ μ L, and the risk was particularly high among men with CD4⁺ counts less than 200/ μ L (15,17). Our data are compatible with these observations. We observed high incidences of both *in situ* and invasive anogenital cancers among patients with low CD4⁺ counts but found no indication of a further increase in risk among patients with CD4⁺ counts below 100/ μ L (median, 33/ μ L in this study) compared with those having CD4⁺ counts greater than or equal to 200/ μ L (median, 270/ μ L).

Rates of *in situ* cancer could be underestimated in patients with severe immunosuppression if life-threatening conditions in

these patients lead to less aggressive screening for anogenital precursor lesions. However, RRs for *in situ* cancers may be generally somewhat overestimated if HIV infection and AIDS lead to increased ascertainment of preinvasive lesions. Taken together, observations in this study and in previous studies suggest that the loss of cell-mediated control over HPV-infected keratinocytes in HIV-infected patients starts at CD4⁺ levels considerably above 200/ μ L. This hypothesis is compatible with the observed excess of anogenital HPV-associated malignancies in other immunocompromised patients, such as renal transplant recipients (46–49).

We recently hypothesized that the increase in tonsillar carcinoma incidence seen in the United States among young men in recent decades (50) might be partly explained by an effect of HIV/AIDS on HPV-associated tonsillar squamous carcinomas (51,52). However, while we found an excess of tonsillar cancer in men with AIDS, no trend toward increasing risk with advancing immunosuppression was seen. We confirm previous reports of squamous cell conjunctival cancer in patients with AIDS (5,53,54); however, again, there was no increasing risk in relation to onset of AIDS. Our estimates of the RR in white and Hispanic males (13- to 26-fold increase) may be conservative, since six (86%) of seven conjunctival cancers were squamous cell carcinomas, whereas background rates used to calculate the expected cancers included only 49% squamous cell variants.

The major strength of our study is the size and population-based nature of the AIDS–Cancer Match Registry. We studied more than 300 000 patients with a total of 314 669 person-years at risk in the early post-AIDS period alone, so we had considerable power to detect even moderately increased risks of rare anogenital malignancies. For comparison, the largest previous study on cancers among AIDS patients (3) had a follow-up period of 40 733 person-years after AIDS.

Our study also has potential limitations. Mismatches between patients in AIDS and cancer registries may have occurred but probably had little impact. We previously used a probabilistic matching algorithm estimated to be 99.2% sensitive and 99.6% specific (6). The current work used commercially available software that improved the efficiency of organizing and linking the files. Thus, the few missed or false matches are unlikely to threaten the validity of our findings.

The survival-conditioned incidence rates for estimating RRs prior to AIDS onset were based on the assumption that cancer patients who are HIV infected (but who have not yet progressed to AIDS) have cancer survival functions identical to those of comparable cancer patients without HIV infection. For *in situ* cancers, this assumption is probably reasonable, but if HIV infection leads to more rapid progression and death from invasive cancer (55,56), our estimates of the expected cancers prior to AIDS may have been too optimistic and thus resulted in too low pre-AIDS estimates of the RR. Even with this bias favoring the finding of spurious trends, we observed no consistent trends for the invasive cancers.

With the exception of anal cancer in homosexual men, data on cancer incidence in HIV-negative subjects with comparable lifestyles are sparse. The crude incidence of invasive anal cancer among homosexual men with AIDS was 23.9 per 100 000 person-years in our study, an estimate that is well within the suggested range of 12.5–36.9 per 100 000 person-years for the general male homosexual population in the United States prior to the AIDS epidemic (57). In another study (58), the incidence of

invasive anal cancer was similar in HIV-positive (13.4 per 100 000 person-years) and HIV-negative (16.6 per 100 000 person-years) homosexual men.

In summary, previous studies have shown an increased incidence of anogenital low- and high-grade SILs among HIV-infected individuals. Reduced ability in the HIV-immunocompromised host to combat cancer-associated HPV infections and altered expression of HPV genes E6 and E7 are possible mechanisms. This study expands the anogenital precancerous spectrum influenced by HIV to include carcinomas *in situ*. However, although HPV-associated invasive cancers also occurred in statistically significant excess, this increase may not be a direct consequence of HIV-mediated immunosuppression. Rather, the progression of anogenital carcinoma *in situ* may depend on the accrual of additional genetic damage occurring at an increased rate in rapidly proliferating epithelial cells with dysfunctioning cell cycle control. Alternatively, progression to invasion may be the result of as yet unknown cofactors with a high prevalence among individuals with, or at risk of, HIV infection and AIDS.

APPENDIX: CONTRIBUTORS AND PARTICIPANTS IN THE AIDS–CANCER MATCH REGISTRY STUDY GROUP

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NOTES

¹The soundex system is an alphanumeric system that codes together names of the same and similar sounds but of variant spellings.

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